A Systematic Review of Three Conditions for Possible Inclusion in the Social Security Administration’s Compassionate Allowances Program.

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Abstract
Exploratory research methods were employed to analyze a number of systems and protocols in place at the SSA, regarding the provision of the Compassionate Allowances List. Literature available in academic databases was reviewed and reported on and was used as empirical evidence demonstrating whether or not a condition invariably met the disability criteria set forth by the Social Security Administration. Based on this systematic review, it was determined that Rubinstein-Taybi syndrome and Smith-Magenis syndrome ‘invariably’ meet the criteria for disability as specified by the Social Security Administration. 22q11 deletion syndrome results in a highly variable disease presentation and individual cases fluctuate widely. Given this, it is suggested that those with 22q11 deletion syndrome proceed through the standard claims process if the individual case warrants disability consideration and benefits.

Analysis of the Problem:

The Social Security Administration (SSA) Compassionate Allowances List began in 2008. This program created a mechanism within the Social Security Disability department for identifying diseases and other medical conditions that by definition meet Social Security’s standards for disability benefits. The program initially identified fifty neurological, mental, and immune disorder conditions that qualified as a disability (under statutory definition provided by SSA) necessitating expedited delivery of benefits; reducing waiting time and more immediate eligibility. Neurodevelopmental conditions result in an impairment in the growth and development of the brain and/or the central nervous systems. There are many neurodevelopmental conditions which are not included in the list of conditions set forth by the Compassionate Allowances criterion. These conditions affect one’s ability to maintain gainful employment, and are variable depending on the level of severity. Depending on the syndrome, the needs of the individuals diagnosed may vary greatly, as would their capacity to maintain employment and their need for expedited benefits. As a result, it is hypothesized that Compassionate Allowances may be necessary for individuals diagnosed with neurodevelopmental conditions, with higher disease burdens, who have been so diagnosed for at least 12 months, and are unable to maintain gainful employment. In addition, the condition itself may impact their quality of life or their life itself. Currently the Compassionate Allowances List includes 200 conditions, though there are many conditions which meet the criterion, including those that are developmental in etiology.

Background and Description of the Problem:

Though only 50 conditions were originally added to the Compassionate Allowances list, the current total of conditions has risen to 200, with 13 new conditions effective as of December 11, 2011, 52 new conditions announced April 11, 2012, and 32 new conditions added December 1, 2012 (Social Security Administration, 2012). Some conditions, neurodevelopmental in nature, are not included in the 200 currently acknowledged conditions. There are also other cases that have been diagnosed, well-established, and verified by objective medical evidence but the benefits process is long-winded and difficult to navigate for parents, guardians, and the individuals receiving services. Though the original fifty conditions were constrained to cancers, brain injuries and conditions considered “rare,” the argument that younger-onset dementias should be added to the list was propelled by the fact that those afflicted can no longer maintain employment (Fried, 2009). This opened the possibility of dialogue and research concerning other conditions that also inhibit the possibility of gainful and significant employment and are
neurodevelopmental from birth or present themselves later in life. Only a few conditions that are
developmental in nature are included in the current list of conditions included in Compassionate
Allowances. Some of these conditions also have varying levels of severity, such as: Angelman
syndrome, Cri du Chat syndrome, Cornelia de Lange and Rett Syndrome.

**Relevant Stakeholders:**

Primary stakeholders include the intended beneficiaries of the expansion of the
Compassionate Allowances list, which in this case may include those diagnosed with Rubinstein-
Taybi syndrome, Smith Magenis syndrome and 22q11.2 deletion syndrome as well as their
families. Rubinstein Taybi Syndrome (RTS) is a genetic syndrome with a prevalence of 1 in
125,000 births worldwide. Both sexes are equally susceptible, as are all racial and ethnic groups
(Oliver, Arron, Powis, & Tunnicliffe, 2011). Smith Magenis Syndrome (SMS) is a rare genetic
disorder, which occurs both in males and females, as well as people of all ethnic origins.
Prevalence is estimated at 1 in 25,000 worldwide, though as diagnostic techniques improve,
researchers believe prevalence may be as high as 1 in 16,000 (Sloneem & Udwin, 2011). 22q11
Deletion Syndrome is one of the most common syndromes resulting from a genetic deletion.
Estimates propose that the minimum incidence is around 1 in 4000 live births worldwide
(Sundram & Murphy, 2011).

Currently the group of claimants to the Compassionate Allowances List represents six
percent (this figure includes QDD claimants as well) of all Social Security Disability Insurance
and Supplemental Social Security claimants, although this would expand as additional conditions
are added to the list (Social Security Administration, 2013). It does not appear that adding
conditions to this list would increase the number of claimants to Social Security in general, but
would rather shift the percentage of those applying for benefits through the typical process and
increase the percentage of those applying for the expedited review.

Additional stakeholders may include advocacy groups such as the National Organization
of Rare Diseases, which has held hearings on additional conditions to be included in the CAL
(until their loss of funding to do so) and has been a proponent of considering additional
conditions for inclusion in the Compassionate Allowances program. Other advocacy groups, that
are condition specific, are included in this set of stakeholders. Researchers and experts that are
working towards additional inclusions under this initiative are not necessarily in an advocacy
position, but their work may have an effect that would be satisfactory to both the primary
stakeholders as well as the advocacy groups. Included in this tier of stakeholders are research
organizations to whom Social Security has delegated responsibility for overseeing and funding
such research. One example is Policy Research Inc., which is funded by the Social Security
Administration through the Disability Determination Process Small Grant Program.

The final set of stakeholders would include the Social Security Administration at the
federal level as they will be the group that would ultimately make a decision about inclusion.
State-level Social Security offices would also be impacted as they would then have to expedite
claims from those with Rubinstein-Taybi, Smith Magenis and Velocardiofacial syndrome
through the use of the CAL selection software. These three conditions, if added to the CAL,
would have to be added to the software system. As of 1995, Social Security is an independent
agency and it is not related to nor subsumed under any other agencies in the federal government
(Social Security Administration, 2013).
**Policy Recommendations and Alternatives:**

New research on each condition in relation to the definition of disability used by the Social Security Administration yielded specific recommendations as to whether the condition should be included in the Compassionate Allowances List. Based on this systematic review, it was determined that Rubinstein-Taybi syndrome and Smith-Magenis syndrome ‘invariably’ meet the criteria for disability as specified by the Social Security Administration. 22q11 deletion syndrome results in a highly variable disease presentation and individual cases fluctuate widely. Given this, it is suggested that those with 22q11 deletion syndrome proceed through the standard claims process if the individual case warrants disability consideration and benefits.

An alternative to using the Compassionate Allowances List in this way may include using the Quick Disability Determination (QDD) process. Under the QDD, conditions or other factors found in the initial information submitted by a claimant is flagged based on easily obtainable information to verify the condition and is highly likely to receive a favorable determination (International Social Security Association, 2009). CAL looks strictly at ones’ diagnosis, whereas the QDD considers the diagnosis as well as a variety of other factors.

**Policy Implementation and Evaluation Issues:**

Currently the CAL includes 200 conditions. When a claimant initiates the claim process with Social Security and states that they have one of these 200 conditions, the computer system known as the Predictive Model (PM) automatically categorizes the condition as a CAL case, and a medical and/or psychological consult is rendered unnecessary. In order to implement this policy with additional conditions, the conditions would need to be added to the PM. For those under 18 years of age, a qualified pediatrician or other medical professional who specializes in a medical specialty relevant to the condition would still need to evaluate the case (Social Security Act § 1614(a)(3)(1)).

According to the Social Security Administration, conditions are added to the CAL based on information received from public outreach, hearings, comments received advocacy groups, medical and scientific expert opinion, and the National Institute of Health (Social Security Administration, 2012). Beginning in 2012, information received from the Disability Determination Process Small Grant Program has also been considered. The first hearing was held in 2007, and the last was held on March 16, 2011. No hearings are currently scheduled.

In terms of evaluating this program, the Social Security Administration reports that the CAL has allowed Social Security to process more claims at a faster speed, eliminating a certain percentage of the backlog. Remedying this backlog was marked as a goal (Strategic Objective: 1.3) in the agency’s 2008-2013 strategic plan (Social Security Administration, 2012). The number of cases that proceeded through the CAL list increased from 3.8 percent in 2009 to 5.8 percent in 2012 (Social Security Administration, 2012, p. 71)

**How New Research Would Inform Policy:**

New research in this area provides an empirical basis for including or not including additional neurodevelopmental conditions in the Compassionate Allowances program beyond those that are currently included (Angelman syndrome, Cri du Chat syndrome, Cornelia de Lange and Rett Syndrome).
Definitions:

**Disability (Adults):** “the inability to do any substantial gainful activity by reason of any medically determinable physical or mental impairment which can be expected to result in death or which has lasted or can be expected to last for a continuous period of not less than 12 months. To meet this definition, you must have a severe impairment(s) that makes you unable to do your past relevant work (see § 416.960(b)) or any other substantial gainful work that exists in the national economy.” §416.905(a)

**Substantial Gainful Activity – SGA:** Substantial gainful activity is work activity that is both substantial and gainful: (a) *Substantial work activity.* Substantial work activity is work activity that involves doing significant physical or mental activities. Your work may be substantial even if it is done on a part-time basis or if you do less, get paid less, or have less responsibility than when you worked before. (b) *Gainful work activity.* Gainful work activity is work activity that you do for pay or profit. Work activity is gainful if it is the kind of work usually done for pay or profit, whether or not a profit is realized § 416.972. As of January 1, 2013, for individuals who are not blind the earnings guidelines are $1,040 a month, or if the individual is blind the earnings cap is $1,740 (Social Security Administration, 2012).

**Disability (Children):** “If you are under age 18, we will consider you disabled if you have a medically determinable physical or mental impairment or combination of impairments that causes marked and severe functional limitations, and that can be expected to cause death or that has lasted or can be expected to last for a continuous period of not less than 12 months.” §416.906

**Compassionate Allowances Initiative:** A way to “quickly identify diseases and other medical conditions that invariably qualify under the Listing of Impairments based on minimal objective medical information.” FR Doc. E9–26194 Filed 10–29–09

Methods:

1. Current processes in place within the Social Security Administration were examined as they relate to approval of conditions for the Compassionate Allowances List (CAL).
2. Rubinstein Taybi Syndrome, Smith Magenis Syndrome, and 22q11 Deletion Syndrome were each compared in relation to Social Security’s definition of disability (Social Security Administration, 2012).
3. Utilizing the criteria for the CAL program, Rubinstein Taybi Syndrome, Smith-Magenis Syndrome, and 22q11 Deletion Syndrome were compared to the CAL criteria to determine if these conditions, invariably, meet the criteria.
4. Literature regarding measuring severity thresholds for Rubinstein Taybi Syndrome, Smith Magenis Syndrome, and 22q11 Deletion Syndrome, respectively, was reviewed to understand how severity and intensity determinations are made currently. Using guidance from the Cochrane Methodology Register (Higgins & Green, 2011), this was accomplished through a systematic review of the literature in bibliographic databases, such as The Cochrane Library, and The Health InterNetwork Access to Research Initiative (HINARI). MEDLINE and EMBASE were used as sources of literature that fulfill the predefined inclusion criteria. Regional electronic databases
were searched in order to gather regional or international literature that may not be indexed on MEDLINE and EMBASE. Subject-specific databases were utilized such as: Applied Social Services Index and Abstracts (ASSIA), Education Resources Information Center (ERIC), and PsycInfo. Citation indexes were explored, such as: the Science Citation Index Expanded. Lastly, information from grey literature, such as conferences attended or conference slides and abstracts were reviewed and this information was provided by the National Technical Information Service. The references cited in identified publications were searched in some instances to locate other pertinent studies and assessments. Search strategies were customized for each database given their use and depth of controlled vocabulary related to the three conditions of concern.

5. In addition to the literature searches noted previously, rate-setting standards (proposed and adopted) for the Commonwealth of Massachusetts were reviewed in relation to potential severity determinations, as well as those currently in place for Medicaid, such as the home and community-based services assessment criterion. These assessment scales provided an understanding for the way in which assessments classify disability or impairment from several different perspectives.

6. Each article meeting the inclusion criteria was rated with a code of 1, 2, or 3. A rating of “1” signifies that the article demonstrates that the condition meets one of the three criteria listed previously. A rating of “2” signifies that the article demonstrates that the condition meets 2 of the 3 criteria listed previously. A rating of “3” signifies that the article meets all 3 of the criteria listed previously. From this analysis, only articles which met all 3 of the criteria were reviewed in the final phase.

7. All articles receiving a score of “3” were reviewed to determine what, if any, severity thresholds were identified in each manuscript rated as a “3.” This synthesis was conducted from the interpretative stance, as defined by Dixon-Woods and colleagues (2005). The end result of this synthesis was not integrative in that it did not seek to aggregate data for analysis, but rather to focus on the conceptual themes around disease burden and severity for Rubinstein Taybi Syndrome, Smith-Magenis Syndrome, and 22q11 Deletion Syndrome as each condition relates to the criteria set forth by the Social Security Administration.

8. Severity and intensity levels for each syndrome previously described were compared to the SSA definition of disability as well as the CAL criteria to determine if severity indices screen in or screen out certain severity levels or entire conditions in relation to the CAL program.

9. Results were compiled in this document, which will be submitted to the Policy Research, Inc. as part of the Disability Determination Process Small Grant Program, funding by the Social Security Administration.
Rubinstein-Taybi Syndrome

Rubinstein-Taybi Syndrome (RSTS) [OMIM 180849] was first described in the literature in 1963 (Rubinstein & Taybi, 1963). RSTS is a rare autosomal dominant genetic syndrome (Chiang, et al., 2009) with a prevalence of one in 100,000 to 125,000 births (Petrij, et al., 2000). Both sexes are equally susceptible, as are all racial and ethnic groups, though boys have incomplete or hindered descent of the testes in 78-100 percent of cases. Diagnosis is usually clinical in nature, and relies heavily on well-documented facial features, such as a small head, a ‘beaked’ nose, small mouth, thick eyelashes and eyebrows, and downward slanting fissures between the upper and lower eyelids (Oliver, Arron, Powis, & Tunnicliffe, 2011). Broad thumbs and toes, short stature (78 percent), and overall retardation in growth are also associated with RSTS (Chiang, et al., 2009). In the uncommon case that RSTS is inherited by a child from the parent, some features tend to be more pronounced, such as dysmorphic features and intellectual disability (Bartsch et al., 2009). Only seven cases of parent-to-child transmission have been reported in the literature thus far (Petrij, 2009), and contain only nine reports of siblings diagnosed with RSTS (Bartsch et al., 2010). Though RSTS is thought to arise from de novo mutations; if RSTS is transmitted intergenerational, germ-line mosaicism is thought to be responsible in some cases (Chiang, et al., 2009).

In addition to the well-documented gastrointestinal issues, constipation affects approximately 40-74 percent of those with RSTS. Dental irregularities occur in 67 percent of those diagnosed with RSTS, and caries are prevalent (15-36 percent) given the difficulties associated with brushing the commonly misshapen or misplaced teeth (Wiley et al., 2003). These characteristics evolve throughout the lifespan and are well-documented at each stage.

Among other medical complications, there appears to be an increased risk for those diagnosed with RSTS to develop cancer, in particular brain tumors and leukemia (De Sario, 2009), as well as a high occurrence of bone fractures. In a sample of 700 patients with RSTS, 17 presented with malignant tumors, while 19 had benign tumors (Miller & Rubinstein, 1995). Intubation and anesthesia pose particular challenges for this population given the placement of their larynx and a laryngeal wall that is susceptible to collapse (Wiley et al., 2003).

Intellectual disability is also associated with RSTS, with some authors theorizing that a lack of development of long-term memory, directly associated with gene mutations, is to blame (De Sario, 2009). The usual range of IQ for those diagnosed with RSTS is 35-50, though variations in these levels have been reported (Wieczorek, Bartsch, Lechno, Kohlhase, Peters, Dauwerse… Passarge, 2009). Although some with RSTS may be more mildly affected, Shawky, Elsayed, & Seifeldin (2012) report that often the severity of intellectual disability causes those with RSTS to be confined to an institutional setting. In fact, up to 74 percent of individuals with RSTS have an IQ less than 50 (Tanaka, Ling, Rubinstein, & Crone, 2006).

One study reported problems with speech in up to 90 percent of those surveyed, including some individuals who are non-verbal and utilizing sign language or augmentative communication devices (Wiley, et al., 2003). Despite these other difficulties, initiating social contact and friendly behavior is considered a strength for those with RSTS (Galéra et al., 2009). When approaching early adulthood, however, behavior changes may occur that can be described as impulsive, aggressive, moody, and anxious (Oliver, Arron, Powis, & Tunnicliffe, 2011). These changes have been described by some authors (Yagihashi, Kosaki, Okamoto, Mizuno, Kurosawa, Takahashi,… Kosaki, 2012) to occur as early as adolescence. Some adults are described as experiencing mood-related disorders, obsessive-compulsive disorders, tic disorders, self-injurious behavior, and features suggestive of autism (Wiley, et al., 2003). While early death
has been reported as a rare occurrence for those with RSTS, it has been noted in cases where a deletion was present and clinical presentation was severe (Bartsch, et al., 1999). Life expectancy generally is reported as normal in the literature (Kumar, Suthar, Panigrahi, & Marwaha, 2012).

**Severity Thresholds:**

Approximately 45-56 percent of RSTS cases appear to occur through a mutation in *CREB Binding Protein*, CREBBP. CREBBP deletions are found in 8-12 percent of patients (Bartsch, et al., 2006), while a rare cause of RSTS appears to be a mutation in the *EIA Binding Protein*, P300 gene (Zimmerman, Acosta, Kohlhase, & Bartsch, 2007), with detection rates at approximately three percent (Chiang, et al., 2009). Diagnosis is still clinical in nature (Chiang, et al., 2009), and relies on the presence of developmental or intellectual disability, broad thumbs, broad great toes, overall hindrance in growth, and abnormalities in the face (Petrij, et al., 2000). Detection of mutations has been absent in approximately 40 percent of those with the clinical diagnosis of RSTS (De Sario, 2009).

**Mild:**

A mild phenotype has been suggested, though these phenotypes are considered to be missense mutations and are rare. In fact, only six mutations of this type have been reported in the literature (Bartsch, Labonté, Albrecht, Wierczorek, Lechno, Zechner, & Haaf, 2009).

EP300 gene mutations are associated with a mild phenotype and are also rare in comparison to CREBBP mutations. In fact, the characteristic broad toes and broad thumbs may be absent in the case of an EP300 mutation. In addition, typical intelligence, and developmentally appropriate height and facial features may be found (Bartsch et al., 2009). Those affected may be misdiagnosed or underdiagnosed (De Sario, 2009). In a sample of 92 patients, only three presented with EP300 gene mutations. In another sample of 38 patients, only one possessed an EP300 mutation (2.6 percent) (Zimmerman, Acosta, Kohlhase, & Bartsch, 2007). In a study of one patient with an EP300 mutation, mild symptoms were reported including a potential for no cognitive limitations, a beaked nose, a narrow and arched palate, an extreme overbite, myopia, and broad fingers and toes. Upon follow-up, it was found that this patient failed the final examination at a school designed for people with learning disabilities, vocational training was not helpful, and she now attends a workshop setting for those with cognitive disabilities. Her IQ is approximately 75 (Zimmerman, Acosta, Kohlhase, & Bartsch, 2007). This presentation appears to be typical for those with an EP300 mutation (Bartsch, Labonté, Albrecht, Wierczorek, Lechno, Zechner, & Haaf, 2009). While this patient originally was thought to possess a mild phenotype, her work capacity indicates that she is unable to engage in substantial gainful employment as a workshop setting typically would not allow a person to earn more than the $1040 required by SSA’s standards.

Ogretmen and Silan (2010) report a case of a 77-year-old woman with learning difficulties but no signs of intellectual disability. Though she possessed many of the characteristic markers of RSTS, she did not have the thumb and toe irregularities. Her main complaint was of pruritis and keloids, and her presentations were distinctive of the mild phenotype, or EP300 mutation in RSTS.

**Severe:**

Bartsch and colleagues (2006) have suggested a new designation for severe Rubinstein-Taybi syndrome or chromosome 16p13.3 deletion syndrome. This form of RSTS resulted in
death in infancy for the three patients under study, and prior to death, failure to thrive, life-threatening infections, and seizures were present. All patients had a CREBBP deletion of a large size and DNASE1 was potentially implicated as well (Bartsch, et al., 2009). In two other studies, children encountered severe complications in the first two weeks of life, which ultimately resulted in death (Bartsch, et al., 2009; citing Kimura et al., 1993 and Bartsch et al., 1999). In one case a 20-month old male without a thymus died after respiratory infections were not amenable to treatment (Kimura et al., 1993). In another case a newborn died after five days of life during surgery to repair a hypoplastic left heart (Hanauer et al., 2002). Cardiac defects frequently occur in RSTS (~33 percent; Bartsch et al., 2006; ~24-38 percent, Wiley, et al., 2003).

In one instance, identical twin girls were both diagnosed with RSTS due to a mutation in the CREBBP gene. Born at 33 weeks, both girls had feeding difficulties accompanied with severe gastroesophageal reflux. Both twins required gastrostomy tubes due to the feeding issues. Twin 1 has a seizure disorder, moderate hearing loss, myopia, spasticity in the lower extremities, and a global developmental delay. Twin 2 experienced an atrial septal defect, hearing loss, myopia, spasticity of the lower extremities, global developmental delay, and autism spectrum disorder. In addition, both twins possessed a Chiari abnormality, which led to rapidly progressive scoliosis. Tonsillar displacement of varying severity was noted in both twins. Scoliosis screening has been recommended for all patients with RSTS, as this group is at risk for cervical vertebral aberrations. In addition, tethering of the spinal cord is also a risk, and may present as a neurogenic bladder, gait abnormalities, and pain in the lower back. The twins, now 13, required surgical interventions, including spinal fusion for one, and Chiari decompression for both (Parsley, Bellus, Handler, & Tsai, 2011). Feeding difficulties are common in this population and have been estimated at 71-80 percent. Seizures are also noted in 27-28 percent of those with RSTS, and abnormal EEG results in 57-66 percent of RSTS individuals (Wiley, et al., 2003).

In addition to the severe physical symptoms associated with RSTS, the average IQ of children and young adults with RSTS in one study (n=50) was approximately 51, with a range of 30-79. In another study, the average IQ was 35.6, with a range of 25-79. In addition, 90 percent were described as having a short-attention span, 65 percent had self-stimulatory behaviors, 86 percent acted younger than their chronological age, 76 experienced difficulty concentrating, and 68 percent liked to be alone (Galerá et al., 2009).

Method:

Using guidance from the Cochrane Methodology Register (Higgins & Green, 2011), a systematic review of the literature on Rubinstein-Taybi syndrome was undertaken. The following databases were searched: The Cochrane Library, The Health InterNetwork Access to Research Initiative (HINARI), MEDLINE, EMBASE, Applied Social Services Index and Abstracts (ASSIA), Education Resources Information Center (ERIC), and PsycInfo. The Science Citation Index Expanded was searched as well as the National Technical Information Service. The references cited in identified publications were searched in some instances to locate other pertinent studies and assessments. Search strategies were customized for each database given their use and depth of controlled vocabulary related to the three conditions of concern.

Using this method, 752 articles were identified through an initial search, with 338 articles reviewed in regard to the inclusion criteria. 62 articles were identified that met at least one of the three criterion set forth by the Social Security Administration in their definition of “disability.” Three articles were subsequently excluded as they did not refer to RSTS specifically enough. Of the 59 articles reviewed during the coding process, 18 articles were coded as a “1”
(demonstrating that the condition will last beyond 12 months), 21 articles were coded as a “2” (demonstrating that the presence of the first criteria plus an impact on quality of life or death), and 20 articles were coded as “3” (demonstrating full disability criteria). See Figure 1 for a visual depiction of this method.

Comparison with SSA Criteria:

1. Lasting for a continuous period of at least 12 months  
   a. Individuals with RSTS can expect the condition to last a lifetime. At this time, there is no cure or treatment for RSTS, though treatment for some of the symptoms is available.

2. Impact quality of life or may result in death  
   a. Those with the most severe symptoms may experience a type of RSTS, which may result in death. As stated previously (Bartsch, et al., 2006; Bartsch, et al., 1999), death is a rare occurrence for those with RSTS, but may result in newborns with a particular constellation of symptoms and/or may result from a deletion in the CREBBP protein. Though death is not a usual occurrence, an impact on one’s quality of life generally occurs.

3. Interferes with substantial gainful employment  
   a. Capacity for substantial gainful employment is difficult to ascertain from the current empirical literature on RSTS, given that it does not tend to be a topic that is explicitly addressed. However, Bishop (2010) derived her own measure of severity. Though her measure was defined only in educational and occupational terms, this four point scale measures the severity of RSTS at 3.50, with 4 being the highest. A 3.50 is equivalent to “Likely to require special schooling; may be employable in adulthood, but likely to need support in daily living” (Bishop, 2010, p. 3). It should be noted that this rating scale does not take into account physical symptoms, though these are addressed in (1.) and (2.) above. This rating does not suggest that an individual cannot be employed, but if the affected individual requires daily support, they also will likely be placed in workshop settings where a percentage of the minimum wage will be earned (see section 14c of the Fair Labor Standards Act), as opposed to a wage that would exceed the SSA standards of $1040 per month.
   b. Stevens, Pouncey, and Knowles (2011) surveyed 32 males and 29 females with RSTS (and/or their families) and found IQ scores ranging from 24-80. Most of this sample continued to live with their parents (69 percent), in group homes (21 percent), or in supervised apartment settings (5 percent). Most of this sample received disability payments (93 percent), and financial support from their parents (61 percent). 73 percent were under guardianship by their parents. Fifty percent of this group had been employed, with 50 percent employed in the community (with support in the food industry, recycling, or Goodwill), and 35 percent working in sheltered workshops. Fifty-eight percent of the sample attended a day habilitation program, signifying a lack of substantial gainful employment and reliance on a Medicaid funded day setting.

Recommendation:
Rubinstein-Taybi syndrome is a condition that will undoubtedly affect individuals for a lifetime, will impact their quality of life significantly, and according to the empirical literature, will substantially limit or prohibit substantial gainful employment. It is recommended that this condition receive strong consideration for addition to the Compassionate Allowances List, especially for those that can provide genetic evidence that they have been diagnosed with RSTS.

Smith-Magenis Syndrome:

Smith-Magenis Syndrome (SMS) (OMIM #182290, *607642) is a rare genetic disorder, which occurs both in males and females, as well as people of all ethnic origins. SMS occurs as a result of a deletion within chromosome 17p11.2 (Udin, Webber, & Horn, 2001). Prevalence is estimated at one in 25,000, though as diagnostic techniques improve, researchers believe prevalence may be as high as one in 16,000. As of 2001, there were 100 cases described in the literature (Udin, Webber, & Horn, 2001), though at least 500 cases have been diagnosed across the world since 1982 (Wolters et al., 2009). In 90 percent of cases a deletion in chromosome 17p11.2 is responsible, and is detectable through in situ hybridization (FISH). In 10 percent of cases, a deletion in RAI1 is detectable (Elsea & Girirajan, 2008).

Distinctive facial features are found in this syndrome, as well as fingers bending inward and small toes. Dental irregularities occur in more than 90 percent of those diagnosed, and in under 40 percent of cases scoliosis, cardiac deficiencies, and renal and thyroid issues may be present. In almost 75 percent of cases, peripheral neuropathy or decreased sensitivity to pain may be an issue and may coincide with the severity of behavioral issues. Evidence of peripheral neuropathy early in life may include hypotonia (in 100 percent of cases), with corresponding hyporeflexia (in 84 percent of cases) and a high pain threshold (Gropman et al., 2006).

Genetic confirmation of the 17p11.2 mutation is one path to diagnosis, though clinical diagnosis is generally initiated by physical and behavioral symptoms. Gropman and colleagues (2006) have suggested that a unique infant phenotype might exist given that these infants typically demonstrate age appropriate disposition and displays of social skills. Some indicative facial features may be present as well as developmental displays, but typical temperament and socialability may lead to a delayed diagnosis. SMS infants also have normal growth in terms of head circumference, height, and weight. At approximately one year of age, a decline is noted in infants with SMS and failure to thrive may be a concern. As infants, and becoming more accentuated with time, a broad and square face is evident, leading to a misdiagnosis of Down Syndrome in some cases. At approximately 18 months, self-injurious behaviors become evident as well as stereotypic behaviors. The prevalence of self-injurious behaviors is 96 percent and well-documented in the literature (Sloneem, Oliver, Udwin, & Woodcock, 2011).

Intellectual disability is generally present, though reports vary in the moderate to severe range. While individuals with SMS demonstrate many skills including attention to detail, computer skills and long-term memory capacity, these strengths may be misleading as adults with SMS require more assistance than might be readily apparent. Some have found that adult daily living skills actually decreased as chronological age increased, which may be in part due to behavioral difficulties such as severe sleep disturbance, impulsivity, physical aggression, and stereotypy (Sloneem & Udwin, 2011). Self-injurious behavior is particularly problematic, as described previously. Unique self-injurious behaviors (SIBs) occurring in SMS patients include onychotillomania (pulling out fingernails and toenails) as well as polyembolokoilamania.
(inserting foreign objects into bodily cavities) (Elsea & Giriajan, 2008). These behaviors have been so severe in some cases that abuse has been suspected and children have been referred to social services (Laje, Morse, Richter, Ball, Pao, & Smith, 2010).

Some authors have attributed SIBs to an inability to communicate (Gropman, et al., 2006; Sloneem, Oliver, Udwin, & Woodcock, 2011). Other authors have argued that these behaviors are maintained by attention, as children and adults with SMS consistently seek out adult contact and attention (Taylor & Oliver, 2008). In addition to self-injurious behavior, other maladaptive behaviors occur at a high frequency, such as: Physical aggression (87.5 percent), destructive behavior (81.3 percent), impulsivity (80 percent), and verbal aggression (43.8 percent). In fact, individuals with SMS were more than 35 times more likely to engage in self-injury as compared to those with intellectual disabilities and far more likely than those with Angelman, Cri du Chat, Cornelia de Lange, Fragile X, and Prader-Willi. SMS individuals were also more than three times more likely to engage in physical aggression than those with intellectual disabilities and more likely than the previously noted conditions. This group was also disproportionately more inclined to hit themselves with their own body or against or with an object, bite themselves or pull on oneself (Arron, Oliver, Moss, Berg, & Burbidge, 2011). These behaviors are noted to occur on an almost daily basis (Sloneem, Oliver, Udwin, & Woodcock, 2011). Gropman and colleagues (2006) note ten behavioral features that distinguish SMS from other syndromes such as Prader-Willi or those arising from mixed etiologies. These ten were determined with 100 percent accuracy and include: “temper tantrums (94 percent), disobedience (97 percent), attention-seeking (100 percent), property destruction (86 percent), impulsivity (86 percent), aggression (57 percent), hyperactivity (94 percent), distractibility (89 percent), toileting difficulties (80 percent), sleep disturbance (94 percent), and nail-biting behaviors (72 percent) (p. 343). In addition to the behaviors noted above, stereotypical behavior is often present and may include “self-hugging” or squeezing the upper body. These behaviors are known to escalate with age, and are correlated with level of intellectual disability and severity of the sleep disturbance (Elsea & Giriajan, 2008).

In addition to the difficulties noted previously, sleep disturbance is a hallmark characteristic of SMS and occurs in 75-100 percent of SMS cases. In these cases, a reversed circadian rhythm is responsible, which is thought to be caused by abnormal melatonin production and integration. Excessive lethargy in the daytime and reduced sleep in the 24 hour cycle are oft-reported symptoms, in addition to early-morning and nocturnal waking. Difficulties with management of sleep have been difficult to overcome, and one uncontrolled study showed promising results with acebutolol, but did not restore nighttime melatonin plasma concentrations (Elsea & Giriajan, 2008).

Severity thresholds:

Though patients with SMS present somewhat homogenously, there are questions of whether severity may be linked to whether SMS is due to a deletion in 17p11.2 or a mutation of RAI1. Patients with RAI1 mutations (10 percent) are reported to experience less of motor delay, compared to those with 17p11.2 deletions. These patients may also be higher-functioning. While their severity may seem mild, these patients often struggle with overeating and obesity issues (~90 percent for weight and height percentiles). In addition, these patients may exhibit higher frequencies of insertion of foreign objects into body cavities, dental and eye irregularities, and upper body squeezing (Elsea & Giriajan, 2008).
Those with small deletions of 17p11.2 may be less likely to exhibit flattened heads, dental and eye irregularities, banging on the head, and hyperactive behavior (Elsea & Giriajan, 2008).

While the prevalence of behavioral difficulties in those with large deletions is decreased, this is due to the fact that large deletions of 17p11.2 may lead to more profound intellectual disability and other mobility-limiting features (Elsea & Giriajan, 2008). Other authors (Finucane, Dirrigl, & Simon, 2001) reported an inverse relationship between level of functioning and severity of self-injurious behaviors. In their study of 29 SMS individuals (age range 1.78 to 49.04 years) an increase level of functioning was correlated with a higher level of severity of self-injurious behaviors.

Though SMS occurs in both males and females, females are more likely to be nearsighted, may have eating disorders, experience coldness in their extremities, and have language difficulties leading to communication issues (Elsea & Giriajan, 2008).

It appears to be difficult to ascertain whether a 17p11.2 deletion leads to a more or less severe presentation than an RAII mutation. While the mutation may appear to cause a milder presentation, other disabling features of the condition offset this and can lead to a severe presentation (Elsea & Giriajan, 2008), which may interfere with one’s capacity for substantial gainful employment.

Method:

Using guidance from the Cochrane Methodology Register (Higgins & Green, 2011), a systematic review of the literature on Smith-Magenis syndrome was undertaken. The following databases were searched: The Cochrane Library, The Health InterNetwork Access to Research Initiative (HINARI), MEDLINE, EMBASE, Applied Social Services Index and Abstracts (ASSIA), Education Resources Information Center (ERIC), and PsycInfo. The Science Citation Index Expanded was searched as well as the National Technical Information Service. The references cited in identified publications were searched in some instances to locate other pertinent studies and assessments. Search strategies were customized for each database given their use and depth of controlled vocabulary related to the three conditions of concern.

Using this method, 794 articles were identified through an initial search, with 780 articles reviewed in regard to the inclusion criteria. 31 articles were identified that met at least one of the three criteria set forth by the Social Security Administration in their definition of “disability.” One article was subsequently excluded as the authors did not refer to SMS specifically enough. Of the 30 articles reviewed during the coding process, four articles were coded as a “1” (demonstrating that the condition will last beyond 12 months), 17 articles were coded as a “2” (demonstrating that the presence of the first criteria plus an impact on quality of life or death), and nine articles were coded as “3” (demonstrating full disability criteria). See Figure 2 for a visual depiction of this method.

Comparison with SSA Criteria:

1. Lasting for a continuous period of at least 12 months
   a. Individuals with SMS can expect the condition to last a lifetime. At this time, there is no cure or treatment for SMS, though treatment for some of the symptoms is available.

2. Impact quality of life or may result in death
a. There is no evidence in the literature that SMS leads to an early demise, and reports of adults living into their 70s exist (Udwin, Webber, & Horn, 2001). There is no doubt that SMS may affect quality of life. Children and adults with SMS appear to be under constant care from others, and appear to be dependent on this care in most cases. There are no reports in the literature of individuals with SMS bearing children, and the majority of study samples continue to live at home with their parents, or in residential care (Sloneem, Oliver, Udwin, & Woodcock, 2011; Finucane, Dirrigl, & Simon, 2001; Udwin, Webber, & Horn, 2001).

3. Interferes with substantial gainful employment
   a. In a sample of 21 individuals diagnosed with SMS, most required support for almost all of their activities of daily living and were described as “dependent on staff” (Udwin, Webber, & Horn, 2001, p. 827). The individuals were unable to travel on their own and 18 could alone be alone for an hour, while 21 could be left alone for only a few minutes.
   b. One adult worked in a shelter workshop setting (which would not result in meeting the $1040 per month benchmark set for substantial gainful employment), while the rest spent their days in day habilitation centers or training workshops. Six attended college courses previously, while six were still attending classes at the time of the study. None of these 21 adults lived independently; residing with their parents (11), group homes or residential community settings (8), and two resided in boarding schools (Udwin, Webber, & Horn, 2001). In another study, approximately 84 percent of the SMS sample lived at home with their parents, while almost 16 percent were cared for in residential care settings (Sloneem, Oliver, Udwin, & Woodcock, 2011).
   c. Gropman and colleagues (2006) note that adults with SMS may rely much more on caregivers than is evident given their moderate intellectual disability.

Recommendation:

Smith-Magenis Syndrome is a condition that will undoubtedly affect individuals for a lifetime, will impact their quality of life significantly, and according to the empirical literature, will substantially limit or prohibit substantial gainful employment. It is recommended that this condition receive strong consideration for addition to the Compassionate Allowances List.

Velocardiofacial Syndrome (VCFS) / 22q11 Deletion Syndrome:

Velocardiofacial Syndrome (VCFS) / 22q11 Deletion Syndrome (OMIM #188400; DiGeorge Syndrome #192430; Velocardiofacial Syndrome #602054) is one of the most common syndromes resulting from a genetic deletion. For the purposes of this report, this syndrome will be referred to as 22q11DS, as this genetic deletion is known by many names (Velocardiofacial Syndrome, DiGeorge syndrome, conotruncal anomalies face syndrome, Cayler syndrome, Sedlačková syndrome and 22q11 deletion syndrome) and referral to the genetic deletion will reduce the use of pseudonyms (Shprintzen, 2008). Estimates propose that the minimum incidence is around one in 4000 live births (Sundram & Murphy, 2011).

There are over 180 characteristics of 22q11DS and as a result genetic testing has been relied upon for accurate diagnosis. Though approximately 87 percent of cases are caused by 3 Mb deletions that are identical among cases, expressions of the syndrome vary widely.
Approximately 7 percent of cases have a smaller deletion of 1.5 million base pairs. In a preponderance of cases, 25 to 30 genes are deleted. In approximately 90 percent of cases, this deletion occurs *de novo* (Antshel, Kates, Roizen, Fremont, & Shprintzen, 2005). Familial transmission is possible, and those respective cases result in severe cognitive impairments and a higher rate of intellectual disability (Zinkstok & van Amelsvoort, 2005). In addition, receptive tasks (taking in information such as listening or reading) were scored significantly lower for those children with a deletion that is maternally derived as opposed to those with a paternally derived deletion (Murphy, 2004). Characteristic facial features of this syndrome include an elongated face, a lengthened pear-shaped nose, small ears, and narrow eyes (Antshel, Kates, Roizen, Fremont, & Shprintzen, 2005).

22q11DS may affect every system in the body, and in its most severe form, may be life-threatening. Cardiac deficits may be present, with congenital heart disease in as many as 75-80 percent of cases (Goldmuntz, 2005), with a ventricular septal defect presenting in 14-18 percent of cases (McElhinney, Driscoll, Levin, Jawad, Emanuel, & Goldmuntz, 2003). In fact, 22q11DS is the most common disorder related to congenital heart defects (Shprintzen, Higgins, Antshel, Fremont, Roizen, & Kates, 2005). TBX1 is an affected transcription factor, and as a result organs that are associated also suffer compromised development (Zemble, Prak, McDonald, McDonald-McGinn, Zackai, & Sullivan, 2010). Hypoparathyroidism is also a common characteristic, diagnosed in 40-75 percent of those with a 22q11.2 deletion. This consists of the total absence of or small parathyroid glands, and may present early in life as hypocalcemia. Seizures may present secondary to hypoparathyroidism and/or hypocalcemia (González & Bautista, 2009).

In addition, immunodeficiency may be present in up to 80 percent of cases, with an increase in susceptibility for an assortment of autoimmune disorders (McLean-Tooke, Spickett, & Gennery, 2007). In some cases this will necessitate thymic transplant in those patients with T-cell deficits (Goldmuntz, 2005). In cases where a T cell deficit is present, mortality rates are high even when appropriate treatment is provided (Sullivan, 2007). Gastrointestinal and ophthalmologic abnormalities (7-70 percent) are common as well (Sullivan, 2007).

22q11DS is also the most common condition associated with cleft palate (Shprintzen, Higgins, Antshel, Fremont, Roizen, & Kates, 2005). In addition, velopharyngeal insufficiency (VPI) may result from a cleft palate. These two conditions often contribute to the speech and language problems seen in those with 22q11.2 DS. In a study of 25 patients with 22q11.2 DS, 84 percent experienced a satisfactory result from palatal lengthening, a procedure used to treat such conditions. Many of those in the sample, however, had difficult cooperating with the pre- and post-operative tests (Widdershoven, Stubenitsky, Breugem, & MinkvanderMolen, 2008).

Temperament of children with 22q11.2 DS varies and has been described as “modestly difficult” (Antshel, Stallone, AbdulSabur, Shprintzen, Roizen, Higgins, & Kates, 2007, p. 218). When parents were asked to rate their children’s temperament as well as their own, their children were found to be less consistent in daily habits, less able to focus or maintain attention, less cheery or agreeable, less likely to continue with an activity for a sustained period of time, and less able to demonstrate a flexible response to change. It was also found that an increase in difference between parent and child temperament resulted in reporting of higher behavioral difficulties in the child (Antshel, Stallone, AbdulSabur, Shprintzen, Roizen, Higgins, & Kates, 2007).

Intellectual disability is often present in the mild to moderate range. In an examination of IQ in 103 with Velocardiofacial syndrome, 60 percent of the children demonstrated borderline to normal intelligence (> 70), while 40 percent exhibited an intellectual disability. Given the wide
range between verbal and performance IQ scores (six to eight points), the effect may be best thought of as a non-verbal learning disability (Sundram & Murphy, 2011). Though verbal scores tend to be higher than performance, those with 22q11.2 DS tend to perform worse on standardized measures of language skill than would be expected (Antshel, AbdulSabur, Roizen, Fremont, & Kates, 2005). It has been estimated that 90-100 percent of children with 22q11.2 deletion syndrome meet the criteria for a learning disability (Sobin, Kiley-Brabeck, Daniels, Khuri, Taylor, Blundell,… Karayiorgou, 2005). In a study specifically addressing basic number processing, children with 22q11 demonstrated slower number processing in terms of comparison, addition, subtraction, and strategizing (De Smedt, Reynvoet, Swillen, Verschaffel, Boets, & Ghesquière, 2009).

Additionally, psychiatric diagnoses are also prevalent and often include: anxiety, depression, attention deficits. Attention deficit/hyperactivity disorder is the most commonly diagnosed psychiatric illness among individuals also diagnosed with 22q11DS (Gothelf, Presburger, Levy, Nahmani, Burg, Berant, Bliede,… Weizman, 2004), and is 30-40 percent higher than the national average (nine percent for children) (Sobin, Kiley-Brabeck, Khuri, & Karayiorgou, 2009). A dual diagnosis of autism spectrum disorder and/or obsessive-compulsive disorder may also occur (Sundram & Murphy, 2011). In a sample of 78 children (ages 7-15 years old) with confirmed 22q11.2 DS and 36 typical controls, the 22q11.2 DS sample presented with higher anxiety scores and this was correlated with lower adaptive functioning (Angkustsiri, Leckliter, Tartaglia, Beaton, Enriquez, & Simon, 2012). In another study of 86 children with 22q11.2 DS and 36 community controls, children with 22q11.2DS were found to have significantly increased scores of somatization, social issues, and thought issues on the Child Behavior Checklist. Manic symptoms were not elevated, as compared to community controls, however, for those with 22q11.2 DS, mania predicted anxiety, somatization, and thought and conduct issues (Aneja, Fremont, Antshel, Faraone, AbdulSabur, Higgins,… Kates, 2007).

Rates of schizophrenia and schizotypy are 25 percent higher than a typical population. 22q11.2 DS is currently one of the highest risk factors for development of schizophrenia, though only 2 percent of those diagnosed with schizophrenia possess the 22q11.2 deletion (Kates, Antshel, Willhite, Bessette, AbdulSabur, & Higgins, 2005). Up to 50 percent of adolescents with 22q11DS report passing psychotic episodes, while approximately 33 percent of adults with 22q11DS are diagnosed with schizophrenia (Armando, Girardi, Vicari, Meghini, Digilio, Pontillo,… Amminger, 2012).

Deficits in working memory and executive function capacity have been demonstrated in the literature, and there is evidence that this may result from the reduction in the prefrontal cortex (which represents 30 percent of total brain volume) by 11 percent in children with 22q11.2 DS. In addition to reductions in the prefrontal cortex, total brain volume is reduced, as well as larger ventricles, and reductions in the temporal lobes and hippocampus with age (Kates, Antshel, Willhite, Bessette, AbdulSabur, & Higgins, 2005).

In a study of 49 children with confirmed 22q11.2 deletion syndrome, 94 percent of the children presented with neuromotor deficits. There were no differences between the younger and older children in the sample, and for 12 of the children these deficits remained stable over a three-year period (Sobin, Monk, Kiley-Brabeck, Khuri, & Karayiorgou, 2006). In a study of 40 children with confirmed 22q11.2 DS, ages 5.2 to 12.9, impairment was found in fine motor agility, kinesthetic cognizance, and visual motor exactness (Sobin, Kiley-Brabeck, Daniels, Khuri, Taylor, Blundell,… Karayiorgou, 2005).
Severity Thresholds:
Severity among phenotypes varies widely among those with 22q11DS. This variability has not been found to correlate with the size of the deletion, given that some individuals with large deletions demonstrate mild presentations, while the reverse is true for others. In one study, monozygotic twins had different presentations, where one twin experienced a cardiac abnormality and the other did not (Gothelf, Presburger, Levy, Nahmani, Burg, Berant, Bliede,…. Weizman, 2004).

In terms of cognitive functioning, some reports note that females experience a sharper decline on psychological tests than males (especially in full scale IQ and performance IQ; Duijff, Klaassen, Swanenburge de Veye, Beemer, Sinnema, & Vorstman, 2012), while others have reported that males in their sample were more cognitively affected than females (Antshel et al., 2010). Antshel and colleagues (2010) provided evidence for the fact that girls appear to have a cognitive advantage over boys, but this lead does not sustain over time and declines with age. De Smedt and colleagues (2007) rejected this finding and not only found that sex did not have an effect, neither did cardiac defects. Overall, the results of a study of 69 children found that overall IQ declined significantly by 9.7 points from 5.5 to 9.5 years for both sexes. The decline was twice as much for verbal IQ as it was for performance IQ (Duijff et al., 2012). As described earlier, in cases where the transmission was familial, cognitive impairments are more severe. It was suggested that this may be due to the lower educational attainment of the parents (De Smedt, Devriendt, Fryns, Vogels, Gewillig, & Swillen, 2007).

Differences have also been noted in regard to prodromal syndromes. One clue to the differential presentation in prodromal symptoms was speculated to arise from a higher ratio of Met alleles versus Val alleles. Though this difference was not statistically significant in the study conducted by Antshel and colleagues (2010), other authors have indicated a higher rate of psychotic symptoms in relation to those with the Met allele. In general, lower performance scores during childhood often predicted prodromal symptoms, as did high levels of anomalous or peculiar behaviors as well as anxiety (Antshel et al., 2010).

As Sobin and colleagues (2009) caution, “For the welfare of the majority of children with 22q11DS that will never develop a severe mental illness, it is essential that conclusions are carefully examined, and pointedly conservative” (p. 9).

Method:
Using guidance from the Cochrane Methodology Register (Higgins & Green, 2011), a systematic review of the literature on 22q11.2 deletion syndrome was undertaken. The following databases were searched: The Cochrane Library, The Health InterNetwork Access to Research Initiative (HINARI), MEDLINE, EMBASE, Applied Social Services Index and Abstracts (ASSIA), Education Resources Information Center (ERIC), and PsycInfo. The Science Citation Index Expanded was searched as well as the National Technical Information Service. The references cited in identified publications were searched in some instances to locate other pertinent studies and assessments. Search strategies were customized for each database given their use and depth of controlled vocabulary related to the three conditions of concern.

Using this method, 1386 articles were identified through an initial search, with 1383 articles reviewed in regard to the inclusion criteria. 84 articles were identified that met at least one of the three criteria set forth by the Social Security Administration in their definition of “disability.” Seven articles were subsequently excluded as they did not refer to RSTS specifically enough. Of the 77 articles reviewed during the coding process, 21 articles were coded as a “1”
(demonstrating that the condition will last beyond 12 months), 49 articles were coded as a “2” (demonstrating that the presence of the first criteria plus an impact on quality of life or death), and seven articles were coded as “3” (demonstrating full disability criteria). See Figure 3 for a visual depiction of this method.

**Comparison with SSA Criteria:**

1. Lasting for a continuous period of at least 12 months
   a. Individuals with a 22q11.2 deletion can expect the condition to last a lifetime. At this time, there is no cure or treatment for Velocardoefacial syndrome, though treatment for some of the symptoms is available.

2. Impact quality of life or may result in death
   a. Due to the multiple body systems affected as a result of 22q11DS, children may be exposed to repeated surgeries and hospitalizations. It has been hypothesized that this negative experience early in life may result in an altered physiological stress response system, and predispose children to later anxiety disorders. Higher anxiety scores and have been correlated with lower adaptive functioning in this population (Angkustsiri, Leckliter, Tartaglia, Beaton, Enriquez, & Simon, 2012) and may be predictive of prodromal symptoms (Antshel et al., 2010).
   
   b. In a British study, 55 out of 504 subjects died as a result of Velocardoefacial syndrome or congenital malformations associated with the syndrome. More specifically, 29 out of 31 deaths due to congenital malformations were cardiovascular malformations. Two deaths were due to malignancies, two were due to metabolic and endocrine issues, two resulted from circulatory system issues, and 31 were related to the digestive system (Swerdlow, Schoemaker, Higgins, Wright, & Jacobs, 2008).
   
   c. In a Canadian study of 100 individuals, three individuals with schizophrenia died at relatively young ages (44, 22, and 52 years of age), and post-mortem autopsies revealed a number of complications for each individual, resulting in their early demise (Kiehl, Chow, Mikulis, George, & Bassett, 2009).

3. Interferes with substantial gainful employment
   a. Angkustsiri, Leckliter, Tartaglia, Beaton, Enriquez, & Simon (2012) discuss the fact that IQ is often relied on as a predictor of adaptive skills. Though this relationship has been studied in other populations, their study was the first to address this correlation in children with 22q11DS. Given that adaptive functioning is necessary to become an independent adult (and sustain substantial gainful employment), this question is important. Fifty-eight percent of the children in Angkustsiri and colleague’s sample demonstrated elevated anxiety scores, with phobia symptoms in 60 percent of the children. This level of anxiety interfered with their adaptive functioning. Moreover, this level of anxiety, especially in those children with obsessive-compulsive disorder (20 percent) was correlated with a higher risk of developing schizophrenia in the following five years. Fabbro, Rizzi, Schneider, Debbane, and Eliez (2012) concur with the previous study. Beaton and Simon (2011) also agree with previous studies, which posit that increased traumatic stress in childhood, owing to the unique and extensive medical involvement and social/ emotional impairments, increases the risk of psychosis later in life.
Recommendation:

While 22q11DS will continue to affect individuals throughout their life, and may even impact their quality of life, or in rare instances, result in death, the syndrome on the whole possesses variability to the extent that it cannot be determined that all who possess the deletion will experience a complete disability. As a result, it cannot be recommended as an addition to the Compassionate Allowances List, though those who cannot manage substantial gainful activity would be encouraged to pursue the disability claims process through the traditional channels. SSA may also consider adding 22q11.2 deletion syndrome to the Quick Disability Determination process to expedite claims for those individuals with severe presentations and disease burdens.

Discussion:

The Compassionate Allowances List provides a benefit to both the Social Security Administration and its respective claimants. By identifying diagnoses that will invariably meet the criterion for disability, claimants may experience an expedited review time and the Social Security Administration can expect to see a decrease in their backlog of applications. This systematic review provided one example of a system to identify those diagnoses that may be considered for inclusion in this initiative. Limitations to this review exist. The time frame for exploration of databases was from 2000-2013. Pertinent literature may be available prior to this timeframe, and this limiter may have excluded evidence. Only available full-text articles written in English were included to provide sufficient review, though steps were taken to procure unavailable manuscripts from two different institutions of higher learning. This systematic review did not utilize meta-analysis techniques, and opted instead for interpretive synthesis (Dixon-Woods, et al, 2005). A future study of this kind utilizing meta-analysis may yield more detailed quantitative results, though this may exclude the single case studies which provided in-depth information on the extent and course of these conditions.

This systematic review provided an in-depth examination of the extent to which the three conditions reviewed invariably meet or fail to meet the definition of disability provided by the Social Security Administration. As a result, it is strongly recommended that Rubinstein-Taybi syndrome and Smith-Magenis syndrome receive consideration for inclusion in the Compassionate Allowances List. Further study regarding 22q11.2 deletion syndrome is recommended.
References:


